ehp ENVIRONMENTAL HEALTH PERSPECTIVES
http://www.ehponline.org

Ambient Fine Particulate Matter and Mortality among Survivors of Myocardial Infarction: Population-Based Cohort Study

Hong Chen, Richard T. Burnett, Ray Copes, Jeffrey C. Kwong, Paul J. Villeneuve, Mark S. Goldberg, Robert D. Brook, Aaron van Donkelaar, Michael Jerrett, Randall V. Martin, Jeffrey R. Brook, Alexander Kopp, and Jack V. Tu

http://dx.doi.org/10.1289/EHP185

Received: 1 April 2015
Revised: 21 December 2015
Accepted: 22 April 2016
Published: 6 May 2016

Environ Health Perspect DOI: 10.1289/EHP185
Advance Publication: Not Copyedited

Ambient Fine Particulate Matter and Mortality among Survivors of Myocardial Infarction: Population-Based Cohort Study

Hong Chen,[1,2,3] Richard T. Burnett,[4] Ray Copes[1,2], Jeffrey C. Kwong,[1,2,3,5] Paul J. Villeneuve,[2, 6] Mark S. Goldberg,[7,8] Robert D. Brook,[9] Aaron van Donkelaar,[10] Michael Jerrett,[11] Randall V. Martin,[10,12] Jeffrey R. Brook,[13] Alexander Kopp,[3] and Jack V. Tu[2,3,14]

[1] Public Health Ontario, Toronto, ON, Canada; [2]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; [3]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [4]Population Studies Division, Health Canada, Ottawa, ON, Canada; [5]Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada; [6]Department of Health Sciences, Carleton University, Ottawa, ON, Canada; [7]Department of Medicine, McGill University, Montreal, QC, Canada; [8]Division of Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada; [9]Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor, MI, USA; [10]Department of Physics and Atmospheric Science, Dalhousie University, Halifax, NS, Canada; [11]Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, CA, USA; [12]Harvard-Smithsonian Centre for Astrophysics, Cambridge, MA, USA; [13]Air Quality Research Division, Environment Canada, Toronto, ON, Canada; [14]Division of Cardiology, Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Address correspondence to Hong Chen, Public Health Ontario, 480 University Avenue, Suite 300, Toronto, Ontario M5G 1V2. Telephone: 647-260-7109. E-mail: hong.chen@oahpp.ca

Running title: Fine particulate matter and survival after AMI

Acknowledgments: The Enhanced Feedback For Effective Cardiac Treatment (EFFECT) study was supported by a Canadian Institutes of Health Research team grant in cardiovascular outcomes research to the Canadian Cardiovascular Outcomes Research Team; it was initially funded by a Canadian Institutes of Health Research Interdisciplinary Health Research Team grant and a grant from the Heart and Stroke Foundation of Canada. This current work was supported by a Canadian Institutes of Health Research operating grant.

Disclaimer: The opinions, results and conclusions reported in this paper do not necessarily represent the views of Institute for Clinical Evaluative Sciences or the Ministry of Health and Long-term Care.

Competing financial interests: We declare that we have no competing financial interests.

Abstract

Background: Survivors of acute myocardial infarction (AMI) are at increased risk of dying within several hours to days following exposure to elevated levels of ambient air pollution. Less is known, however, about the influence of longer-term air pollution exposure on survival after AMI.

Objective: We conducted a population-based cohort study to determine the impact of long-term exposure to fine particulate matter ($PM_{2.5}$) on post-AMI survival.

Methods: We assembled a cohort of 8,873 AMI patients who were admitted to one of 86 hospital corporations across Ontario, Canada in 1999-2001. Mortality follow-up for this cohort extended through 2011. Cumulative time-weighted exposures to $PM_{2.5}$ were derived from satellite observations based on participants' annual residence during follow-up. We used standard and multilevel spatial random-effects Cox proportional hazards models, adjusting for potential confounders.

Results: Between 1999 and 2011, we identified 4,016 non-accidental deaths, of which 2,147 were from any cardiovascular disease, 1,650 from ischemic heart disease, and 675 from AMI. For each 10-$\mu g/m^3$ increase of $PM_{2.5}$, the adjusted hazard ratio (HR_{10}) of non-accidental mortality was 1.22 (95% confidence interval (CI): 1.03-1.45). The association with $PM_{2.5}$ was robust to sensitivity analyses and appeared stronger for cardiovascular-related mortality: ischemic heart (HR_{10}=1.43; 95%CI: 1.12-1.83) and AMI (HR_{10}=1.64; 95%CI: 1.13-2.40). We estimated that 12.4% of non-accidental deaths (or 497 deaths) could have been averted if the lowest measured concentration in an urban area (4-$\mu g/m^3$) had been achieved at all locations over the course of study.

Conclusions: Long-term air pollution exposure adversely affects the survival of AMI patients.

INTRODUCTION

Acute myocardial infarction (AMI) is one of the most common cardiovascular events, affecting ~7.9 million adults in the U.S. (Roger et al. 2011) and 540,000 in Canada (Chow et al. 2006).

Once people develop AMI, their chance of long-term survival and their quality of life are reduced substantially (Roger et al. 2011). Recent studies showed that people with an AMI had induced ST segment depression (Mills et al. 2007), decreased heart-rate variability (Park et al. 2005; Zanobetti et al. 2010), and increased ischemic events (Pope et al. 2006) within several days after exposure to elevated level of air pollution. People with an AMI have also been found to be at higher risk of dying when daily pollution levels increase, especially with particulate matter ≤10μm in diameter (PM_{10}) (Bateson and Schwartz 2004; Berglind et al. 2009; Von Klot et al. 2005). These findings are supported by toxicological studies linking pollution with increased systemic oxidative stress and inflammation, blood coagulability, progression of atherosclerosis, and reduced heart-rate variability (Brook et al. 2010), implicating that AMI patients may be particularly sensitive to air pollution exposure (O'Neill et al. 2012; Sacks et al. 2011).

Less is known, however, about the influence of longer-term (months to years) exposure to air pollution on mortality after AMI, although there is growing evidence that longer-term exposure result in substantially larger health risks than exposure over several days (Brook et al. 2010). Among a small set of studies that have assessed the influence of long-term exposure to air pollution on mortality after AMI, three studies reported increased all-cause mortality in association with exposure to $PM_{2.5}$ (Tonne and Wilkinson 2013), PM_{10} (Zanobetti and Schwartz 2007), and elemental carbon (Von Klot et al. 2009). However, in two other studies no compelling evidence was found for associations with $PM_{2.5}$ (particles ≤2.5μm in diameter) (Koton et al. 2013) or nitrogen dioxide (NO_2) (Rosenlund et al. 2008). Because cause-of-death

information was unavailable in previous studies (Tonne and Wilkinson 2013; Von Klot et al. 2009; Zanobetti and Schwartz 2007), it remains uncertain about the specificity of the association between air pollution and post-AMI mortality which is helpful in understanding pathways linking long-term exposure with survival in this subpopulation.

We thus conducted a population-based cohort study to evaluate the impact of long-term exposure to $PM_{2.5}$ on survival among AMI patients. In addition, we sought to quantify the burden of post-AMI mortality attributed to $PM_{2.5}$. Given the high prevalence of AMI and the ubiquity of air pollution, such information may help target interventions to improve outcomes for AMI patients.

METHODS

Study Design and Study Population

We conducted a cohort study of newly admitted AMI patients participating in phase 1 of the Enhanced Feedback For Effective Cardiac Treatment (EFFECT) study (1999-2001) (Tu et al. 2009), a large randomized trial in Ontario, Canada. Details of the EFFECT study have been presented elsewhere (Tu et al. 2009). Briefly, that study included all patients admitted to one of 86 hospital corporations in Ontario with a primary or most responsible diagnosis of AMI (*International Classification of Diseases, Ninth Revision*, ICD-9 code 410). Trained nurses abstracted demographic (*e.g.*, marital status) and clinical information (*e.g.*, smoking status, laboratory tests, and medical history) from patients' primary charts. After review of the medical records, those who: (1) fulfilled the European Society of Cardiology/American College of Cardiology clinical criteria (Alpert et al. 2000); (2) had AMI onset before arriving at hospital; and (3) were registered with Ontario's provincial health insurance plan were included (Tu et al. 2009). Patients transferred from other acute-care facilities were excluded.

We restricted the study population to those who were ≥35 years of age at hospital admission, had a length of hospital stay of ≥2 days, and were Canadian-born individuals. Consistent with previous studies of air pollution and post-AMI survival (Berglind et al. 2009; Rosenlund et al. 2008; Tonne and Wilkinson 2013; Von Klot et al. 2005), we further restricted to those who were alive for at least 28 days after hospital discharge.

The Research Ethics Board of Sunnybrook Health Sciences Center, Toronto, approved the study.

Outcomes

The follow-up period was from the 29th day after discharge in 1999-2001 until the end of 2011. We ascertained underlying cause of death and date of death using record linkage to the Ontario Registrar General's Death database using the patients' unique, encrypted health card number (linkage rate: 98%). The primary outcome was non-accidental mortality (*ICD* codes are listed in Supplemental Material, Table S1). To evaluate the specificity of the association between air pollution and mortality, we also ascertained deaths from any cardiovascular disease, ischemic heart disease, and AMI, respectively. In addition, to detect possible bias due to unmeasured confounding and other errors that may lead to spurious inference, we considered negative control outcomes for which no (or weaker) associations with air pollution were expected (Lipsitch et al. 2010). For this, we identified deaths from accidental causes and non-cardiopulmonary, non-lung cancer causes (Jerrett et al. 2013).

Assessment of Ambient Concentrations of $PM_{2.5}$

Estimates of ground-level concentrations of $PM_{2.5}$ were derived from satellite observations of aerosol optical depth, a measure of light extinction by aerosols in the total atmospheric column, in conjunction with information from a global atmospheric chemistry transport model (GEOS-

Chem CTM) (van Donkelaar et al. 2014). We used estimates from 2001 to 2010, thus obtaining 10-year mean concentrations of $PM_{2.5}$ at a resolution of approximately 10×10 km and covering North America below 70°N, which includes all of Ontario (Figure 1). These satellite-based estimates of $PM_{2.5}$ closely agree with ground measurements at fixed-site stations across North America (Pearson correlation coefficient r=0.76, n=974) (van Donkelaar et al. 2014), and they improve the accuracy and spatiotemporal coverage of our earlier satellite-based estimates of $PM_{2.5}$ (van Donkelaar et al. 2010) which have been used to determine the associations of $PM_{2.5}$ with mortality and morbidity (Chen et al. 2013; Crouse et al. 2012), as well as the global disease burden attributable to air pollution (Lim et al. 2012).

The location of residence for each participant during the follow-up was obtained from the Registered Persons Database, a registry of all Ontario residents with health insurance (Chen et al. 2013). Location was refined to the spatial scale provided by six-character postal codes, which in urban areas represent a city block or a large apartment complex. We created annual estimates of exposure to $PM_{2.5}$ for each participant by interpolating the 10-year mean concentrations of $PM_{2.5}$ to the centroid of their residential postal code for that year, thereby accounting for residential mobility. This approach assumes that the spatial pattern in $PM_{2.5}$ did not change appreciably during the follow-up (Miller et al. 2007; Pope et al. 2002). This is a reasonable assumption because we have shown previously that areas in Ontario with higher concentrations of $PM_{2.5}$ have retained their spatial ranking from 1996 to 2010 and that variability in longer-term exposure to $PM_{2.5}$ is primarily spatial rather than temporal (Chen et al. 2013).

Covariates

We *a priori* selected the following potential confounders, abstracted from medical records: age; sex; marital status; employment status (employed/unemployed/retired/homemaker/disabled);

major cardiac risk factors (including smoking status, family history of coronary artery disease, diabetes, hyperlipidemia, hypertension, stroke, previous AMI, previous percutaneous coronary intervention [PCI]); AMI type (ST elevation/non-ST elevation [STEMI/non-STEMI]); acute pulmonary edema; selected comorbidities (including angina, cancer, dementia, dialysis, chronic obstructive pulmonary disease); and cardiovascular medications at hospital discharge including statins, aspirin, ACE inhibitor, and beta-blockers. To assess in-hospital care, we obtained information about the length of hospital stay (days) and the characteristics of attending physicians (cardiologist/internist/family physician) and hospitals (teaching/community/small) (Tu et al. 2009). In addition, to assess the severity of AMI, we calculated the Global Registry of Acute Cardiac Events risk score (GRACE) based on age, history of congestive heart failure and AMI, heart rate, systolic blood pressure, and several other prognostic variables (Bradshaw et al. 2006). We also derived body mass index (BMI: kg/m^2) using self-reported height and weight.

Using 2001 Canadian Census Tract data (see Supplemental Material), we derived three neighborhood-level variables: (1) percentage of population $\geq$15 years of age with less than high school education; (2) unemployment rate; and (3) mean household income. To control for region-scale spatial patterns in mortality that might be caused by factors other than pollution, we created a dichotomous variable classifying Ontario into the Greater Toronto Area, a densely-populated urban mega-region, and all other areas. Toronto tends to differ from other areas in Ontario with respect to socioeconomic and demographic characteristics, health care, and mortality rate (see Supplemental Material, Table S2).

Statistical Analysis

Standard and multilevel spatial random-effects Cox proportional hazards models (Ma et al. 2003) were used to assess post-AMI mortality in relation to $PM_{2.5}$. The spatial random-effects model

accounted for the possibility that patterns of health of residents living in the same or neighbouring communities were more similar than for individuals living further apart, and that these patterns may not be completely explained by variables included in the model. This modeling approach has been used extensively in previous studies of pollution-related mortality in the U.S. (Jerrett et al. 2013; Pope et al. 2002; Pope et al. 2004) and Canada (Crouse et al. 2012).

Consistent with previous studies (Crouse et al. 2012), the random effects in our spatial random-effects Cox model were represented by two levels of spatial clusters, with a first cluster level defined by census divisions (equivalent to counties) and a second level defined by census tracts within census divisions. We assumed that two census divisions were correlated if they were adjacent, as were census tracts within each census division. Census tracts in different census divisions were assumed to be uncorrelated.

We developed models for mortality from non-accidental causes, cardiovascular (any, ischemic heart, AMI), and as negative controls, accidental and non-cardiopulmonary, non-lung cancer causes. We stratified the baseline hazard function by single-year age groups and region, allowing each category to have its own baseline hazard. We included participants with nonmissing information on exposure and covariates, except for marital status (~3% of the cohort had unknown values), employment status (6%), smoking (12%), and BMI (41%) for which we created a separate category of missing values to avoid losing substantial statistical power.

We measured follow-up time (in days) from baseline until death (47%), ineligibility for provincial health insurance (2%), or end of follow-up (51%). We fitted $PM_{2.5}$ as a time-varying variable by modeling time-weighted exposure from baseline until death, with weights for each individual defined by the time spent at each residence. We constructed a sequence of models including different potential confounding factors (see Supplemental Material, Figure S1). The

final model included variables for sex, marital status, employment status, smoking status, family history of coronary artery disease, diabetes, hyperlipidemia, hypertension, stroke, previous PCI, previous AMI, GRACE risk score, AMI type, acute pulmonary edema, indicators for in-hospital care, medications at discharge, comorbidities, and ecological variables. We adjusted for regional variations in the ecological variables across Ontario using the average for each census division and the difference between the values for each census tract and the census division mean. Due to considerable missing data for BMI (41%), we did not include it in the main model, but considered it in a sensitivity analysis.

We tested for deviations from the proportional hazards assumption by adding the cross product of each variable with the natural logarithm of the time variable, but we did not find any violations of this assumption (p>0.05). We also verified the assumption of linearity for all continuous variables by using natural cubic spline functions with up to four degrees of freedom (df). We examined plots of concentration-response curves for $PM_{2.5}$ and computed the Akaike Information Criteria (AIC) to determine whether the response function was non-linear. Since there was no evidence of departure from linearity for the relation of $PM_{2.5}$ and mortality (see Figure 2 and Supplemental Material, Table S3), we report adjusted hazard ratios (HR) and 95% confidence intervals (CI) for each 10μg/m^3 increase of $PM_{2.5}$ (referred to as HR_{10}).

Sensitivity Analyses

We performed a series of sensitivity analyses by considering follow-up starting one year after discharge, controlling for BMI in a subcohort with complete information, restricting analysis to those living outside Toronto, and controlling for population density at the census division level. In addition, we further controlled for distance to nearest acute-care hospitals using a natural cubic spline with 3 df, adjusted for coronary revascularization during follow-up as a time-

varying variable, and adjusted for a categorical variable indicating the population size of participants' home community (rural, <30,000, 30,000-99,999, 100,000-499,999, ≥500,000). We obtained information about coronary revascularization through data linkage to the Discharge Abstract Database and the Ontario Health Insurance Plan Claims Database (Chen et al. 2013).

As well, to account for time trends in air pollution and mortality, we additionally controlled for calendar time using a natural cubic spline with 3 df. To investigate whether the hazard ratios might be influenced by any possible spatial dependence introduced by hospitals, we further added a frailty term (random effect) for hospitals to allow for the possibility that the effect estimates vary from hospital to hospital in the estimation of the main effect and its variance. A gamma distribution for random effect was assumed, with an exchangeable correlation structure within hospitals. We compared the models with and without a frailty term using the AIC. Furthermore, we additionally controlled for neighborhood-level deprivation, density of family physicians, and several other geographically-variable sociodemographic and health-care indicators, as well as restricting to cohort members living between 41.7^{o} N and 46.0^{o} N, where the vast majority of the Ontario population resides, and to those living within 5 km from any manufacturing or process facilities releasing particulate matter (see Supplemental Material).

Lastly, we investigated *a priori* whether individuals with preexisting angina, AMI, diabetes, and hypertension were at greater risk, as well as potential effect modification by AMI type (STEMI/non-STEMI) and medication use, by assessing whether the interaction term that was the cross-product of each variable with $PM_{2.5}$ value was statistically important.

Burden Attributable to $PM_{2.5}$

To quantify the burden of death attributed to long-term exposure to $PM_{2.5}$ among those with AMI, we estimated the number of deaths due to $PM_{2.5}$ with reference to an alternative

(counterfactual) distribution of exposure (*i.e.*, the minimum that could be achieved at the population level). For this, we chose the lowest concentration of $PM_{2.5}$ measured across all cities worldwide (4-μg/m^3) (Brauer et al. 2012). We then derived the attributable fraction and applied it to the number of non-accidental deaths during follow-up (see Supplemental Material). We used the hazard ratio from the fully-adjusted spatial random-effects model. To estimate the 95% uncertainty interval, we sampled the 2.5th and 97.5th percentile of 1,000 draws from the distribution of exposure and the hazard ratio, using the approach from the Global Burden of Disease Study 2010 (Lim et al. 2012).

Analyses were conducted using the R statistical package (version 3.0.0, 64-bit). The spatial random-effects Cox model was fitted using the Cox-Poisson program (Krewski et al. 2009).

RESULTS

Among the 10,386 eligible patients from the EFFECT study, we excluded 84 (~1%) patients who were <35 years old, 379 (4%) whose length of hospital stay was shorter than two days, 281 (3%) who were landed immigrants, 284 (3%) who died within 28 days post-discharge, and 485 (5%) with missing data on covariates except for marital status, employment status, smoking, and BMI, leaving a total of 8,873 patients in our analytical cohort.

At the time of entry, the mean age was 66.9 years, 65% were men, and 36% were current smokers (Table 1). Of the cohort, 23% had a prior AMI, nearly half was diagnosed with STEMI, and 34.5% were prescribed statins at discharge. Average unemployment among the census tracts was 6%, and mean household income was $CDN52,400.

The cohort contributed 72,101 person-years of observation, with a mean follow-up of 8.1 years. During the follow-up, ~39% of participants changed their address, and 22% moved out of the

city that they lived in when enrolled. The average concentration of $PM_{2.5}$ according to participants' residences at baseline was 10.7-μg/m^3 (range, 2.2-16.5), with the highest average concentrations in southern Ontario (Figure 1). Between 1999 and 2011, we identified 4,016 deaths from non-accidental causes, of which 2,147 were from any cardiovascular disease, 1,650 from ischemic heart disease, and 675 from AMI. In addition, there were 121 deaths due to accidents and 1,382 from non-cardiopulmonary, non-lung cancer causes.

We found a positive association for non-accidental mortality using the standard Cox model, with a hazard ratio of 1.12 (95%CI: 0.98-1.29) with each 10-μg/m^3 increase in $PM_{2.5}$, after adjusting for age and sex (Table 2). The corresponding HR_{10} from the random-effects model was 1.14 (95%CI: 0.99-1.32). Controlling for smoking, diabetes, AMI type, GRACE risk score, medication use, and several other individual-level factors strengthened the association in both models (HR_{10}=1.18 for the standard Cox model and HR_{10}=1.20 for the random-effects model). In models adjusting for all individual- and neighborhood-level covariates, the HR_{10} from the standard Cox model was 1.21 (95%CI: 1.03-1.41) and the HR_{10} from the random-effects model was 1.22 (95%CI: 1.03-1.45). Since the estimates were similar between the two models, only results from the random-effects model are reported below, because it allowed for more accurate estimation of statistical error.

In sensitivity analyses, the HR_{10} estimates were not altered appreciably after considering follow-up starting one year after discharge, adjusting for distance to nearest hospitals, adjusting for coronary revascularization during follow-up, adding a frailty term for hospitals to allow for potential spatial clustering, or other sensitivity analyses, with the exception of controlling for BMI (Table 3 and Supplemental Material, Table S4). We found a stronger association for non-

accidental mortality in the subcohort with information on BMI (HR_{10}=1.46, 95%CI: 1.18-1.81), after further controlling for BMI.

We also observed stronger associations between $PM_{2.5}$ exposure and mortality from cardiovascular disease (HR_{10}=1.35, 95%CI: 1.09-1.67), ischemic heart disease (HR_{10}=1.43, 95%CI: 1.12-1.83), and AMI (HR_{10}=1.64, 95%CI: 1.13-2.40) (Table 4). No association was found for mortality from accidental and non-cardiopulmonary non-lung cancer causes. Furthermore, an analysis of selected subgroups did not provide compelling evidence supporting effect modification of $PM_{2.5}$ by diabetes (*p*-interactions varied from 0.06 to 0.90, depending on the outcomes), AMI type (*p*-interactions: 0.07 to 0.33), statins (*p*-interactions: 0.43 to 0.98), and other selected characteristics.

Lastly, we calculated that the rate of mortality would be reduced by 12.4% (95%CI: 1.6%-22.5%) if this cohort had been exposed to the lowest measured level of $PM_{2.5}$ in an urban area, as opposed to their present distribution of exposure. This estimate translates to 497 (95%CI: 65-904) deaths attributable to elevated $PM_{2.5}$ exposure in this cohort.

DISCUSSION

In this cohort study of AMI patients, exposure to ambient $PM_{2.5}$ was associated with increased non-accidental mortality, with HR_{10} varying between 1.21 (95%CI: 1.03-1.41) and 1.22 (95%CI: 1.03-1.45), depending on model structures. The association was robust to sensitivity analyses and appeared to be stronger for mortality from cardiovascular causes, especially ischemic heart disease (HR_{10}=1.43) and AMI (HR_{10}=1.64). Additionally, we did not find strong evidence for effect modification by selected characteristics such as comorbidities and secondary prevention measures. Overall, our estimated association of $PM_{2.5}$ and mortality translates to 497 deaths in

this cohort (or 12.4% of non-accidental deaths) that could be averted if the lowest measured concentration in an urban area (4-$\mu g/m^3$) had been achieved over the course of study.

Few studies have investigated the relationship between post-AMI mortality and long-term air pollution exposure. In a cohort study of 154,204 AMI survivors in England and Wales, with follow-up from 2004 to 2010, Tonne *et al.* (2013) reported an adjusted HR_{10} of all-cause mortality with $PM_{2.5}$ of 1.20 (95%CI: 1.04-1.38) and a HR of 1.01 (95%CI: 0.98-1.04) per 10-$\mu g/m^3$ of NO_2. A second study of 1,120 AMI survivors in central Israel reported a positive but statistically insignificant association of $PM_{2.5}$ with post-AMI mortality (HR_{10}=1.3, 95%CI=0.8-2.1) (Koton et al. 2013). Similarly, two separate cohort studies in the U.S. linked increased all-cause deaths among AMI patients to PM_{10} (Zanobetti and Schwartz 2007) and elemental carbon (a proxy for traffic particles) (Von Klot et al. 2009). In contrast, no association was found for NO_2 with post-AMI survival in an Italian cohort of AMI patients (Rosenlund et al. 2008).

Our risk estimates for $PM_{2.5}$ and mortality appeared higher than those reported previously from cohort studies based on general populations (Cesaroni et al. 2013; Crouse et al. 2012; Hoek et al. 2013; Jerrett et al. 2013; Laden et al. 2006; Pope et al. 2004). In a Canadian national cohort study following 2.1 million adults over 1991-2001, Crouse *et al.* (2012) reported positive associations of $PM_{2.5}$ and mortality from non-accidental causes (HR_{10}=1.15), any cardiovascular disease (HR_{10}=1.16), and ischemic heart disease (HR_{10}=1.31). A meta-analysis of 11 cohort studies examining air pollution and cardiovascular-related mortality reported a pooled HR_{10} of 1.11 (95%CI: 1.05-1.16) for $PM_{2.5}$ (Hoek et al. 2013). While there is some overlap in estimates of risk between this and these previous studies (Cesaroni et al. 2013; Crouse et al. 2012; Hoek et al. 2013; Laden et al. 2006; Pope et al. 2004), the stronger risk estimates observed in this cohort, especially for cardiovascular-related mortality, suggest that AMI survivors are more susceptible

to air pollution than the general population. It is noteworthy that ambient concentrations of $PM_{2.5}$ in Ontario (annual mean in 2000: 11.2-μg/m^3) were considerably lower than that observed in many cities in the U.S. (*e.g.*, annual mean $PM_{2.5}$ in Los Angeles: 20.7-μg/m^3 in 2000) (Coogan et al. 2012), Europe (*e.g.*, Rome, Italy: 19.9-μg/m^3 in 2010) (Cesaroni et al. 2013), and in Asia (*e.g.*, Beijing, China: 56.0-μg/m^3 in 2010 and Deli, India: 153.0-μg/m^3 in 2013) (World Health Organization 2014). Given that billions of people worldwide are exposed to higher concentrations of $PM_{2.5}$ and that the relation between mortality and $PM_{2.5}$ was found similar over a range of exposures in this and previous studies (Burnett et al. 2014), our findings can have important public health implications globally. Our findings imply that important health benefits can be achieved by efforts to further reduce ambient air pollution worldwide.

We did not find strong evidence that comorbidities and medications altered the association between $PM_{2.5}$ and mortality, because power to detect differences was limited. Cardiovascular medications such as statins improve endothelial function, modulate inflammatory responses, maintain plaque stability, and prevent thrombus formation, which potentially protect against $PM_{2.5}$ effects (Delfino et al. 2009; McCracken et al. 2010; Schwartz et al. 2005). Further investigation of potential interaction between cardiovascular medications and air pollution exposure in post-AMI survival is merited, given their widespread use in this subpopulation.

The strengths of this study include its relatively large size and population-based representation of AMI patients in Ontario, the most populous province in Canada. As well, we obtained extensive individual-level information including detailed clinical data and demographic and behavioral characteristics, which allowed for better control for known risk factors. Aspects of our analytic approach also reduce concerns about confounding, such as the use of spatial random-effects models. The standard Cox model yielded smaller estimates of the standard error for $PM_{2.5}$

compared to the spatial random-effects model, suggesting that there was unexplained spatial variation in mortality within the cohort. By specifying nested spatial clusters to account for possible spatial dependencies among participants, the spatial random-effects models improved the estimation of standard error for $PM_{2.5}$ effects. In addition, our study benefited from having information on cause of death, allowing for $PM_{2.5}$-mortality association to be analyzed in more detail. Furthermore, the use of satellite-based long-term average estimates of $PM_{2.5}$ ensures virtually complete spatial coverage of $PM_{2.5}$ of the cohort.

Several limitations merit mention. First, we lacked information on individual socioeconomic status (SES) such as income and education. However, we controlled for smoking, employment status, area-level SES, and comorbidities, which may partly lie in the causal pathway between individual SES and post-AMI mortality (see Supplemental Material, Figure S1). Although we cannot rule out the possibility of residual confounding by individual SES, it is unlikely that this would substantially bias our risk estimates. The null association with negative control outcomes did not support this possibility.

Second, the spatial pattern of $PM_{2.5}$ was derived for the period 2001 to 2010, covering most of the follow-up (1999-2011). We have shown previously that the spatial gradients of ambient $PM_{2.5}$ in Ontario are stable over time and that variability in $PM_{2.5}$ concentrations is primarily spatial rather than temporal (Chen et al. 2013). Because 78% of cohort members never moved or moved only within the city of residence, the spatial contrasts in $PM_{2.5}$ over 2001-2010 are expected to be a reasonable representation of longer-term spatial exposures to $PM_{2.5}$ in Ontario (Chen et al. 2013).

Third, the 10×10 km resolution of satellite-based exposure surface reduced our ability to capture finer-scale intra-urban variation in $PM_{2.5}$ exposures that tends to occur in areas with relatively

high concentrations. This may potentially result in larger uncertainties on characterizing concentration-response relationship at the higher end of $PM_{2.5}$ exposures. We also did not have information on daily activity. Given the inherent imprecision of the spatially-derived exposure, our assessment of exposure was likely subject to nondifferential misclassification that may have attenuated the estimates. In addition, our analyses did not consider the mixture of air pollutants to which subjects may have been exposed.

Fourth, information on most potential confounding variables was obtained at baseline only. Although we adjusted for medications at discharge and coronary revascularization during the follow-up, we could not further account for post-discharge medications because information was unavailable.

In this study, the strongest associations with $PM_{2.5}$ appear to be for cardiovascular-related mortality, especially from ischemic heart disease. This finding supports that the biological pathways involved in the cardiovascular effects of $PM_{2.5}$ (Brook et al. 2010), including systemic oxidative stress and inflammation, increased blood coagulability, enhanced thrombosis, and vascular dysfunction, may have played an important role in increasing post-AMI mortality. These responses may have a greater impact on individuals who already have cardiovascular system compromised, such as AMI patients.

Conclusions

In summary, this study adds weight to previous observations that AMI patients are susceptible to the effect of air pollution and provides new evidence that the survival of AMI patients may be significantly influenced by long-term exposure to $PM_{2.5}$, even at the relatively low levels observed in Ontario.

References

Alpert JS, Thygesen K, Antman E, Bassand JP. 2000. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 36:959-969.

Bateson TF, Schwartz J. 2004. Who is sensitive to the effects of particulate air pollution on mortality? a case-crossover analysis of effect modifiers. Epidemiology 15:143-149.

Berglind N, Bellander T, Forastiere F, von KS, Aalto P, Elosua R, et al. 2009. Ambient air pollution and daily mortality among survivors of myocardial infarction. Epidemiology 20:110-118.

Bradshaw PJ, Ko DT, Newman AM, Donovan LR, Tu JV. 2006. Validity of the GRACE (Global Registry of Acute Coronary Events) acute coronary syndrome prediction model for six month post-discharge death in an independent data set. Heart 92:905-909.

Brauer M, Amann M, Burnett R, Cohen A, Dentener F, Ezzati M, et al. 2012. Exposure assessment for estimation of the global burden of disease attributable to outdoor air pollution. Environ Sci Technol 46:652-660.

Brook RD, Rajagopalan S, Pope CA3, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121:2331-2378.

Burnett RT, Pope CA 3rd, Ezzati M, Olives C, Lim SS, Mehta S, et al. 2014. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. Environ Health Perspect 122:397-403.

Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M, et al. 2013. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. Environ Health Perspect 121:324-331.

Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, et al. 2013. Risk of Incident Diabetes in Relation to Long-term Exposure to Fine Particulate Matter in Ontario, Canada. Environ Health Perspect 121:804-810.

Chow CM, Donvan L, Manuel DG, Johsen H, Tu JV. Regional variation in self-reported heart disease prevalence in Canada. Can J Cardiol. 21:1265-1271.

Coogan PF, White LF, Jerrett M, Brook RD, Su JG, Seto E, et al. 2012. Air Pollution and Incidence of Hypertension and Diabetes Mellitus in Black Women Living in Los Angeles. Circulation 125:767-772.

Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, et al. 2012. Risk of Nonaccidental and Cardiovascular Mortality in Relation to Long-term Exposure to Low Concentrations of Fine Particulate Matter: A Canadian National-Level Cohort Study. Environ Health Perspect 120:708-714.

Delfino RJ, Staimer N, Tjoa T, Gillen DL, Polidori A, Arhami M, et al. 2009. Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. . Environ Health Perspect 117:1232-1238.

Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, et al. 2013. Long-term air pollution exposure and cardio- respiratory mortality: a review. Environ Health doi: 10.1186/1476-069X-12-43.

Jerrett M, Burnett RT, Beckerman BS, Turner MC, Krewski D, Thurston G, et al. 2013. Spatial Analysis of Air Pollution and Mortality in California. Am J Respir Crit Care Med 188:593-599.

Koton S, Molshatzki N, Yuval, Myers V, Broday DM, Drory Y, et al. 2013. Cumulative exposure to particulate matter air pollution and long-term post-myocardial infarction outcomes. Prev Med. 57:339-344.

Krewski D, Jerrett M, Burnett RT, Ma R, Hughes E, et al. 2009. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Res Rep Health Eff Inst 140:5-114.

Laden F, Schwartz J, Speizer FE, Dockery DW. 2006. Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 173:667-672.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2224-2260.

Lipsitch M, Tchetgen TE, Cohen T. 2010. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 21:383-388.

Ma R, Krewski D, Burnett RT. 2003. Random effects Cox models: a Poisson modelling approach. Biometrika 90:157-169.

McCracken J, Baccarelli A, Hoxha M, Dioni L, Melly S, Coull B, et al. 2010. Annual ambient black carbon associated with shorter telomeres in elderly men: Veterans Affairs Normative Aging Study. Environ Health Perspect 118:1564-1570.

Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356:447-458.

Mills NL, Tornqvist H, Gonzalez MC, Vink E, Robinson SD, Soderberg S, et al. 2007. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. N Engl J Med 13;357:1075-1082.

O'Neill MS, Breton CV, Devlin RB, Utell MJ. 2012. Air pollution and health: emerging information on susceptible populations. Air Qual Atmos Health 5:189-201.

Park SK, O'Neill MS, Vokonas PS, Sparrow D, Schwartz J. 2005. Effects of air pollution on heart rate variability: the VA normative aging study. Environ Health Perspect 113:304-309.

Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287:1132-1141.

Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109:71-77.

Pope CA 3rd, Muhlestein JB, May HT, Renlund DG, Anderson JL, Horne BD. 2006. Ischemic heart disease events triggered by short-term exposure to fine particulate air pollution. Circulation. 114:2443-2448.

Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. 2011. Heart disease and stroke statistics-2011 update: a report from the American Heart Association. Circulation 123:e18-e209.

Rosenlund M, Picciotto S, Forastiere F, Stafoggia M, Perucci CA. 2008. Traffic-related air pollution in relation to incidence and prognosis of coronary heart disease. Epidemiology 19:121-128.

Sacks JD, Stanek LW, Luben TJ, Johns DO, Buckley BJ, Brown JS, et al. 2011. Particulate matter-induced health effects: who is susceptible? Environ Health Perspect 119:446-454.

Schwartz J, Park SK, O'Neill MS, Vokonas PS, Sparrow D, Weiss S, et al. 2005. Glutathione-S-transferase M1, obesity, statins, and autonomic effects of particles: gene-by-drug-by-environment interaction. Am J Respir Crit Care Med172:1529-1533.

Tonne C, Wilkinson P. 2013. Long-term exposure to air pollution is associated with survival following acute coronary syndrome. Eur Heart J 34:1306-1311.

Tu JV, Donovan LR, Lee DS, Wang JT, Austin PC, Alter DA, et al. 2009. Effectiveness of public report cards for improving the quality of cardiac care: the EFFECT study: a randomized trial. JAMA 302:2330-2337.

van Donkelaar A, Martin RV, Brauer M, Boys BL. 2014. Use of Satellite Observations for Long-Term Exposure Assessment of Global Concentrations of Fine Particulate Matter. Environ Health Perspect doi:10.1289/ehp.1408646.

van Donkelaar A, Martin RV, Brauer M, Kahn R, Levy R, Verduzco C, et al. 2010. Global estimates of ambient fine particulate matter concentrations from satellite-based aerosol optical depth: development and application. Environ Health Perspect 118:847-855.

Von Klot S, Gryparis A, Tonne C, Yanosky J, Coull BA, Goldberg RJ, et al. 2009. Elemental carbon exposure at residence and survival after acute myocardial infarction. Epidemiology 20:547-554.

Von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti, et al. 2005. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. Circulation 112:3073-3079.

World Health Organization. Burden of disease from Ambient Air Pollution for 2012. http://www.who.int/phe/health_topics/outdoorair/databases/AAP_BoD_results_March2014.pdf?ua=1. [Accessed March 29, 2015].

Zanobetti A, Gold DR, Stone PH, Suh HH, Schwartz J, Coull BA, et al. 2010. Reduction in heart rate variability with traffic and air pollution in patients with coronary artery disease. Environ Health Perspect 118:324-330.

Zanobetti A, Schwartz J. 2007. Particulate air pollution, progression, and survival after myocardial infarction. Environ Health Perspect 115:769-775.

Table 1. Baseline characteristics of study population

Baseline Characteristics [a]	Cohort (N=8,873)
Demographic characteristics	
Age, y	66.9±13.0
Men, %	65
Marital status, %	
Married	68
Single	6
Separate, widowed, or divorced	23
Unknown	3
Employment, %	
Employed/Self	26
Homemaker	3
Retired	62
Unemployed	1
Disabled	2
Unknown	6
Cardiac risk factors and history	
Smoking, %	
Never smoker	28
Current smoker	36
Former smoker	24
Unknown	12
Body mass index, kg/m^2	27.9±5.5
<18.5 (%)	1
18.5-24.9 (%)	17
25.0-29.9 (%)	25
≥30.0 (%)	16
Unknown (%)	41
Family history of coronary artery disease, %	33
Diabetes, %	25
Hyperlipidemia, %	32
Hypertension, %	46
Previous percutaneous coronary intervention (PCI), %	3
Previous myocardial infarction, %	23
Stroke, %	7
GRACE risk score [b]	142±36
Comorbidities, %	
Angina	32
Cancer	3
Dementia	3

Baseline Characteristics [a]	**Cohort (N=8,873)**
Dialysis	1
Chronic obstructive pulmonary disease (COPD)	1
Clinical risk parameters, %	
ST elevation myocardial infarction (STEMI)	49
Acute pulmonary edema	5
In-hospital care	
Length of stay, day	8.0±7.8
Specialty of attending physician, %	
General practice	34
Internal medicine	31
Cardiology	35
Characteristics of hospitals, %	
Teaching	13
Community	80
Small	7
Cardiovascular medication at discharge, %	
Statins	35
Aspirin	78
ACE inhibitor	55
Beta-blockers	70
Area-level characteristics [c]	
Percentage population aged ≥15 y with under high school education	29
Percentage population aged ≥15 y without employment	6
Average household income (Can$1000)	52.4±23.7

[a] Values are percent or mean ± standard deviation

[b] GRACE, Global Registry of Acute Coronary Syndromes.

[c] At the Canadian Census Tract level.

Table 2. Association of non-accidental mortality with every 10-μg/m^3 increase of $PM_{2.5}$

	Standard Cox model		Random-effects model [a]	
Model	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**
$PM_{2.5}$ adjusted for sex and stratifying age and region [b]	1.12	0.98 - 1.29	1.14	0.99 - 1.32
+ Marital status, employment [c]	1.14	1.00 - 1.30	1.15	1.00 - 1.33
+ Cardiac risk factors and history [d]	1.16	1.01 - 1.33	1.16	0.99 - 1.36
+ Clinical severity parameters [e]	1.14	0.99 - 1.32	1.14	0.97 - 1.34
+ Length of stay, characteristics of physicians and hospitals	1.21	1.05 - 1.40	1.22	1.04 - 1.43
+ Medication use at hospital discharge [f]	1.20	1.03 - 1.39	1.21	1.03 - 1.43
+ Preexisting angina, cancer, dementia, COPD, dialysis	1.18	1.02 - 1.36	1.20	1.02 - 1.41
+ Area-level variables [g]	1.21	1.03 - 1.41	1.22	1.03 - 1.45

[a] A nested, spatial random-effects Cox model comprising two levels of spatial clusters: a first cluster level defined by census divisions and a second level by census tracts.

[b] Region: living or not in the Greater Toronto Area.

[c] Variables were added to the model including base model and all previous variables labeled with "+".

[d] Included smoking, family history of coronary artery disease, diabetes, hyperlipidemia, hypertension, stroke, previous PCI, AMI, and GRACE risk score.

[e] Included STEMI/Non-STEMI and acute pulmonary edema.

[f] Included statins, aspirin, ACE inhibitor, and beta-blockers.

[g] Included census division-level unemployment rate, education, and annual household income, as well as the subtraction of these variables at the census tract level from their census-division mean.

Table 3. Sensitivity analyses for the association of non-accidental mortality with every 10-μg/m^3 increase of $PM_{2.5}$

Sensitivity Analysis	No. of deaths	Non-accidental mortality [a]	
		Hazard Ratio	95% CI
Follow-up starting one year after discharge	3,301	1.19	0.99 - 1.40
Restricted to participants with complete data on BMI	2,213	1.46	1.18 - 1.81
Restricted to participants outside Toronto	3,046	1.28	1.06 - 1.58
Adjusted for population density [b]	4,016	1.30	1.07 - 1.58
Adjusted for distance to nearest acute-care hospitals	4,016	1.22	1.03 - 1.46
Adjusted for coronary revascularization during follow-up	4,016	1.22	1.02 - 1.44
Adjusted for long-term time trend in calendar year	4,016	1.23	1.03 - 1.46
Adjusted for indicators for urban size [c]	4,016	1.28	1.06 - 1.55
Added a random effect for hospitals to further investigate spatial dependency as a source of bias	4,016	1.21	1.01 - 1.46

[a] A nested, spatial random-effects Cox model, stratified by age and region, and adjusted for sex, marital status, employment, smoking, family history of coronary artery disease, diabetes, hyperlipidemia, hypertension, stroke, previous PCI, AMI, GRACE risk score, STEMI/Non-STEMI, acute pulmonary edema, in-hospital care, medications, comorbidities, and area-level variables.

[b] At the Canadian Census Division level.

[c] Size of subjects' home community: rural/farm; small town (<30,000); Urban 3 (30,000-99,999); Urban 2 (100,000-499,999); and Urban 1 (>499,999).

Table 4. Associations of cause-specific mortality with every 10-μg/m^3 increase of $PM_{2.5}$

			Fully-adjusted Model [a]	
Cause of death	**ICD-9 code**	**No. of deaths**	Hazard ratio	95% CI
Any cardiovascular	401-459	2,147	1.35	1.09 - 1.67
Ischemic heart	410-414	1,650	1.43	1.12 - 1.83
Myocardial infarction	410	675	1.64	1.13 - 2.40
Non-cardiopulmonary, non-lung cancer	<401, 520-799, and not 162	1,382	1.06	0.81 - 1.39
Accidental	≥800	121	1.07	0.41 - 2.76

[a] A nested, spatial random-effects Cox model, stratified by age and region, and adjusted for sex, marital status, employment, smoking, family history of coronary artery disease, diabetes, hyperlipidemia, hypertension, stroke, previous PCI, AMI, GRACE risk score, STEMI/Non-STEMI, acute pulmonary edema, in-hospital care, medications, comorbidities, and area-level variables.

Figure Legends

Figure 1. Mean satellite-derived estimates of $PM_{2.5}$ across Ontario, Canada, 2001-2010.

Figure 2. Concentration-response relationship between the concentration of $PM_{2.5}$ and nonaccidental mortality during 13-year follow-up after acute myocardial infarction. The hazard ratios were estimated by comparing to 2.2-μg/m^3. The city-mean concentrations of $PM_{2.5}$ of four selected cities in Ontario and the current Canadian Ambient Air Quality Standards (CAAQS, objectives for annual mean concentration: 10-μg/m^3) and the U.S. National Ambient Air Quality Standards (NAAQS, standards for annual mean concentration: 12-μg/m^3) on $PM_{2.5}$ are indicated.

Figure 1.

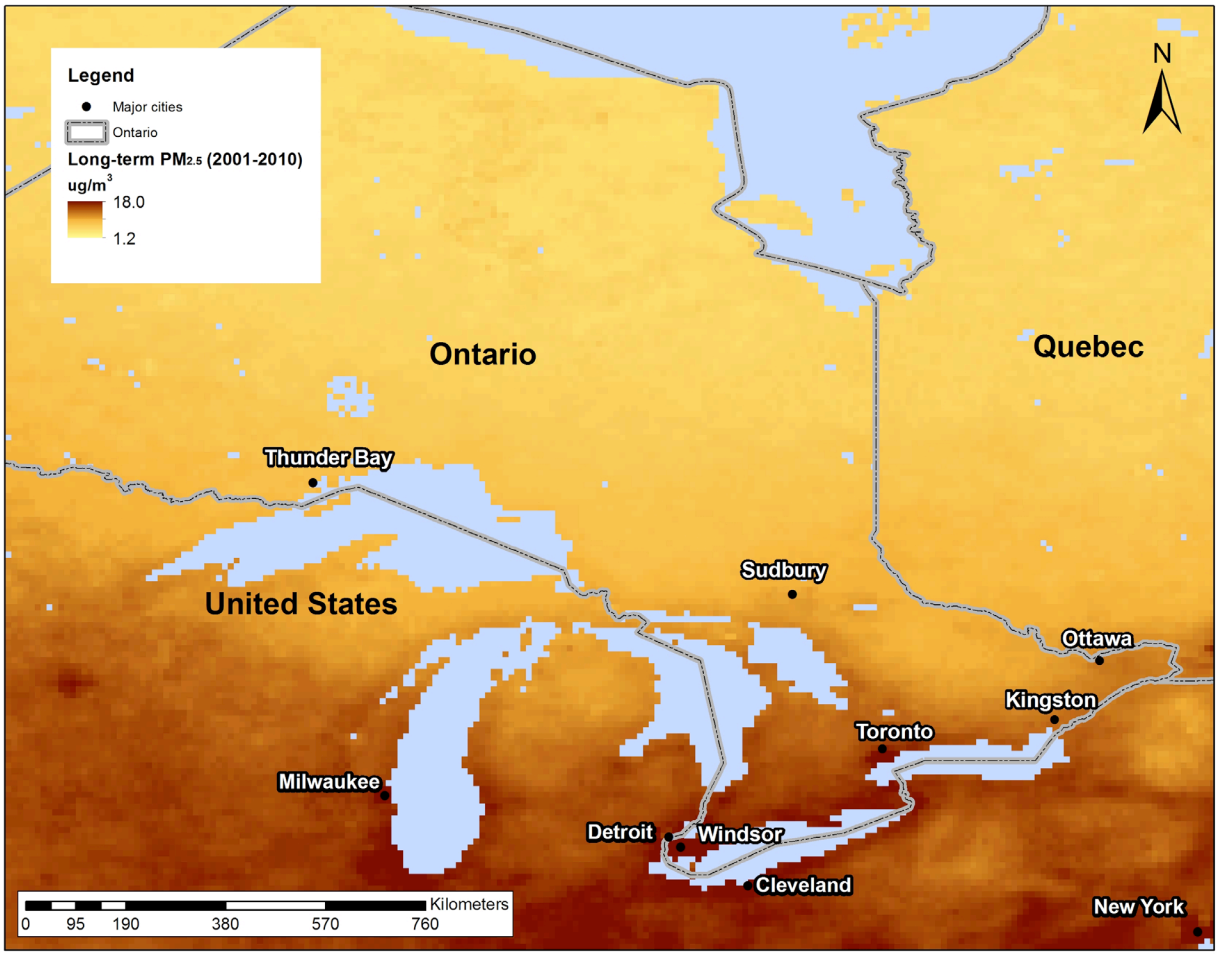
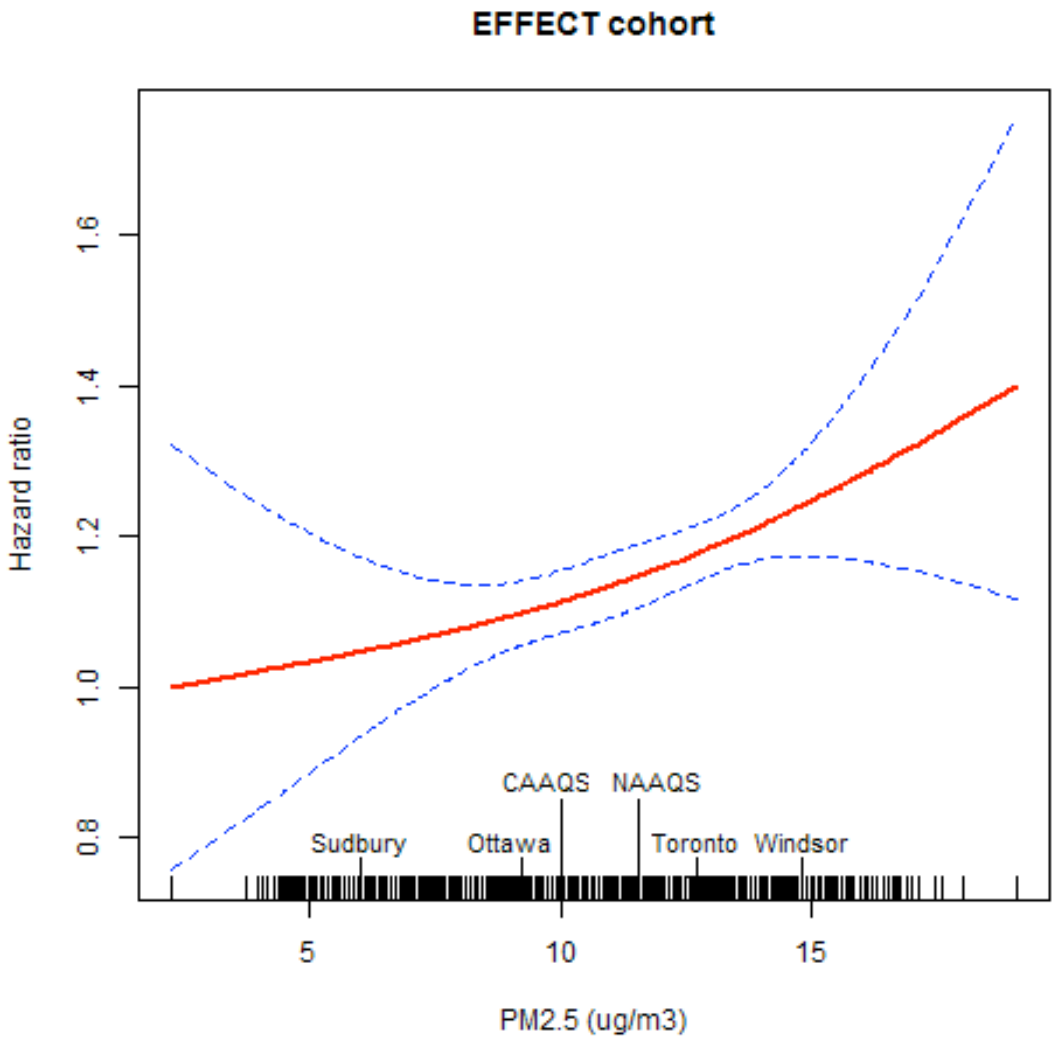

Legend
Major cities
Ontario
Long-term PM2.5 (2001-2010)
ug/m3
18.0
1.2
N
Ontario
Quebec
Thunder Bay
Sudbury
United States
Ottawa
Kingston
Toronto
Milwaukee
Detroit
Windsor
Cleveland
New York
Kilometers
0 95 190 380 570 760

Figure 2.


EFFECT cohort
Hazard ratio
0.8
1.0
1.2
1.4
1.6
CAAQS
NAAQS
Sudbury
Ottawa
Toronto
Windsor
5
10
15
PM2.5 (ug/m3)